

## REMARKS

The claims in the application are 1-20 and Claims 21-23 added by the present amendment.

Favorable reconsideration of the application as amended is respectfully requested.

Concerning the question about priority claim raised in paragraph 2 on page 2 of the Office Action, it is respectfully pointed out the priority claim in the above-identified U.S. national phase application has been made within the time limit set forth in 37 C.F.R. §1.55(a)(1)(ii) and is listed upon the Official Filing Receipt mailed November 9, 2004 (a copy of this Official Filing Receipt is enclosed). Additionally, a copy of the previously-executed Declaration/Power of Attorney is also enclosed for the Examiner's convenience.

Another copy of Form PTO-1449 is enclosed. It is respectfully requested the three non-patent literature citations also be made of record. Please contact the undersigned attorney should these three citations happen to be missing from the file at the Patent and Trademark Office (the Office Action was silent in this regard).

Claims 21-23 added herein find clear support throughout the present application and drawings. More specifically, Claims 21 and 22 find support in Figs. 1-3, the accompanying description in the specification and Claim 10, while Claim 23 finds support in Fig. 4 and the accompanying description at pages 13-15 of the specification. Accordingly, the only outstanding issue is the prior art rejection of the claims.

All Claims 1-20 have been rejected under 35 U.S.C. §103 as obvious over U.S. Pat. Pub. 2001/0055529 to Wixforth in paragraphs 3-21 of the enclosed Office Action. Wixforth belongs to assignee Advalytix AG and corresponds to DE 100 55 318 cited in

both the present application and International Search Report only under category “Y” against Claim 2. The Examiner acknowledges Wixforth fails to teach controlling the titration quantity 17 to be smaller than the analyte drop 1, but asserts such control would be obvious in light of the teachings in Wixforth (hence the obviousness rejection under 35 U.S.C. §103).

However, it is respectfully submitted the present invention as recited in all pending claims herein is patentable over Wixforth, for the following reasons (reference will be made to preferred embodiments of the present invention illustrated in the drawings of the present application).

The present invention is directed to a method of titration in which an analyte 1 is contacted with a quantity of titrant 3 and a parameter changing during reaction between titrant 3 and analyte 1 is studied. More particularly, the present invention provides a titration method that is reproducible even with extremely small volumes of liquid in the range of one nanoliter to a few microliters.

These and other advantages are attained by the claimed method in which a drop of the analyte 1 held together by its surface tension is applied to a substantially flat surface 7 of a solid, especially a solid chip 5, with a titration quantity 17 of the titrant 3 smaller than quantity of the analyte drop 1 then brought into contact with the analyte drop 1. A characteristic quantity for the reaction between the titrant 3 and analyte drop 1 is measured during or after the reaction and, if necessary, another small titration quantity 17 of the titrant 3 is brought into contact with the analyte drop 1 to determine change in the measured quantity with increasing quantity of titrant 3.

With the present invention, need for reaction vessels which could negatively influence titration, e.g., by adhesion, is eliminated. Edge interaction with side walls of a

vessel has been eliminated. Macroscopic titration can be reduced by several orders of magnitude and successfully carried out, e.g., on a small chip 5.

In one preferred embodiment (Figs. 1-3), the titration quantity 17 is separated from a larger quantity of titrant 3 situated on an anchor point 16 connected to a path 18 leading to the analyte drop 1 through a constriction 14 narrower than both the anchor point 16 and path 18, by generating external force to move the titration quantity 17 over the constriction 14 towards the analyte drop 1. In another preferred embodiment (Fig. 4), the titration quantity 17 is separated from a larger quantity of titrant 3 situated on the anchor point 16 by being moved at least once, preferably to and fro, over a region 41 of the surface 7 more strongly wetted by the titrant 3 than surrounding surface and smaller than contact area of the titrant 3 with the surface 7.

Wixforth fails to teach or suggest the claimed invention, for the following reasons.

While Wixforth teaches using interdigital transducers 1, 27, etc. for generating surface acoustic waves to move small quantities of liquid, as even acknowledged by the Examiner *supra*, Wixforth fails to teach controlling a titration quantity 17 to be smaller than the analyte drop 1. While Wixforth might disclose mixing two liquids A and B (Fig. 2 and paragraphs [0041] and [0081]), there is no teaching or suggestion in Wixforth of controlling discrete quantities of the mixed liquids A + B. Titration is not mentioned in this reference. Paragraph [0041] of Wixforth simply discloses driving two liquids towards one another. Paragraph [0054] of Wixforth also simply discloses bringing two small quantities of liquid into contact to be mixed.

In this regard, Wixforth fails to suggest the step of separating the titration quantity 17 from the titrant 3 positioned on the surface 7 in the manner of the present invention. Paragraph [0039] of Wixforth simply discloses dividing a quantity of liquid into two subquantities. Paragraph [0046] of Wixforth just generally discloses separating at least one quantity of matter from the rest, either before or after analysis. Paragraph [0077] of Wixforth just relates to the embodiment shown in Fig. 1, namely providing a surface wave 17 of greater strength to separate a quantity of matter in region 5 of the chip 2 and transport this quantity of matter to reservoir 13.

As set forth *supra*, the present invention is directed to titration of liquids, namely improving titration with minute quantity of liquid, e.g., in the range of one nanoliter to a few microliters. Such small quantities of liquid are required for titration to determine, e.g., the endpoint, as precisely as possible.

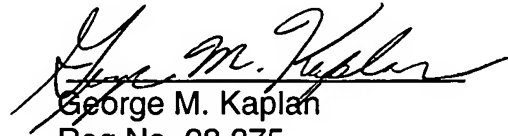
While Wixforth discloses moving drops of liquid along a surface, nevertheless Wixforth fails to disclose application to titration of liquid, much less titration controlled in the improved manner of the presently claimed invention. Accordingly, one skilled in the art looking to improve titration would not even consider Wixforth, to begin with. The only teaching of improving titration in the claimed manner is found in the present application. Therefore, the citation of Wixforth, at most, constitutes mere hindsight reconstruction of the present invention in light of the disclosure found in the present application and cannot be used to reject any claims pending herein.

The remaining art of record has not been applied against the claims and will not be commented upon further at this time.

Accordingly, in view of the forgoing amendment and accompanying remarks, it is respectfully submitted all claims pending herein are in condition for allowance. The requisite fee for the additional claims introduced herein is enclosed.

Early favorable action is earnestly solicited.

Respectfully submitted,

  
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